PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/015266	02.05.2005	30.04.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K49/00 A61K49/18 A61K49/14 A61K49/08 A61K49/04

Applicant
UNIVERSITY OF FLORIDA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Dullaart, Anwyn Telephone No. +31 70 340-3290

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/015266

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 18-40 in part

because:

☒ the said international application, or the said claims Nos. 18-40 in part relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/015266

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-50
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	18-50

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III.

Claims 18-40 partially relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

1. Reference is made to the following documents:

D1: WO 01/89585 A (BIOCRYSTAL LTD [US]) 29 November 2001 (2001-11-29)

D2: Dubertret B et al: "In vivo imaging of quantum dots encapsulated in phospholipid micelles"
Science, Vol. 298, no. 5599, 29 November 2002 (2002-11-29), pages 1759-1762, XP002255863 ISSN: 0036-8075

D3: Yang H et al: "Efficient and photostable ZnS-passivated CdS:Mn luminescent nanocrystals"
Advanced Functional Materials, Vol. 14, no. 2, February 2004 (2004-02), pages 152-156, XP001046237 ISSN: 1616-301X

D4: Yang Heesun et al: "Enhanced photoluminescence from CdS:Mn/ZnS core/shell quantum dots"
Applied Physics Letters, Vol. 82, no. 12, 24 March 2003 (2003-03-24), pages 1965-1967, XP012033608 ISSN: 0003-6951

D5: Tanaka M: "Photoluminescence properties of Mn-doped II-VI semiconductor nanocrystals"
Journal of Luminescence, Vol. 100, no. 1-4, December 2002 (2002-12), pages 163-173, XP004396347 ISSN: 0022-2313

D6: Ballou B et al: "Noninvasive imaging of quantum dots in mice"
Bioconjugate Chemistry, Vol. 15, no. 1, January 2004 (2004-01), pages 79-86, XP001047128 ISSN: 1043-1802

D7: Gao X et al: "Molecular profiling of single cells and tissue specimens with quantum dots"
Trends in Biotechnology, vol. 21, no. 9, September 2003 (2003-09), pages 371-373, XP004450443 ISSN: 0167-7799

D8: Larson D R et al: "Water-soluble quantum dots for multiphoton fluorescence imaging in vivo"
Science, Vol. 300, no. 5624, 2003, pages 1434-1436, XP008053308 ISSN: 0036-8075

D9: Wu X et al: "Immunofluorescent labeling of cancer marker Her2 and other cellular targets with semiconductor quantum dots"
Nature Biotechnology, vol. 21, January 2003 (2003-01), pages 41-46, XP008053284 ISSN: 1087-0156

D10: Chan W C W et al: "Luminescent quantum dots for multiplexed biological detection and imaging"
Current Opinion in Biotechnology, Vol. 13, no. 1, February 2002 (2002-02), pages 40-46, XP002256995 ISSN: 0958-1669

D11: Kim S et al: "Near-infrared fluorescent type II quantum dots for sentinel lymph node mapping"
Nature Biotechnology, vol. 22, no. 1, January 2004 (2004-01), pages 93-97, XP008053357 ISSN: 1087-0156

D12: Jaiswal J K et al: "Long-term multiple color imaging of live cells using quantum dot bioconjugates"
Nature Biotechnology, vol. 21, no. 1, January 2003 (2003-01), pages 47-51, XP009065963 ISSN: 1087-0156

D13: Akerman M E et al: "Nanocrystal targeting in vivo"
Proceedings of the National Academy of Sciences of the USA, vol. 99, no. 20, 16 September 2002 (2002-09-16), pages 12617-12621, XP001182896 ISSN: 0027-8424

2. These documents describe the following.

2. 1. Document D1 discloses fluorescent nanocrystals of the formula CdX core/YZ, in which X=Se, S or Te, Y=Cd or Zn et Z=S or Se. For X and Z = S and Y=Zn, this results in the presently claimed quantum dots (QD), with the exception of the Mn.

2. 2. Document D2 discloses CdSe/ZnS QD used for in vivo imaging.

2. 3. Document D3 discloses the preparation of CdS:Mn/ZnS QD.

2. 4. Document D4 discloses the preparation of CdS:Mn/ZnS QD. Its preparation follows the scheme used for CdSe:Mn/ZnS QD.

2. 5. Document D5 discloses the preparation of CdS:Mn/ZnS QD.

2. 6. Document D6 discloses the use of CdSe/ZnS QD for in vivo imaging.
2. 7. Document D7 discloses the use of CdSe/ZnS QD for the labelling of single cells, and in vivo imaging.
2. 8. Document D8 discloses the use of QD for in vivo imaging. The images obtained are shown in e.g. figure 2. The lack of toxicity of the Cd-containing particles is explained on page 1436, middle column.
2. 9. Document D9 discloses the use of CdSe/ZnS QD for in vivo imaging. The QD are conjugated to an antibody directed to Her2, allowing cancer imaging.
2. 10. Document D10 discloses the preparation of several different QD, and their use for in vivo imaging.
2. 11. Document D11 discloses the use of other QD for imaging the lymphatic system
2. 12. Document D12 discloses cellular imaging using QD.
2. 13. Document D13 describes the use of targeted nanocrystals in in vivo imaging and therapy.

3. Due to the general wording of present claim 1, D3 to D5 seem to oppose novelty in the sense of Article 33.2 PCT.

4. The closest prior art for the remaining claims can be found in documents D1, D2 and D6 to D13, each describing a different prior use of QD in in vivo imaging.
4. 1. The subject-matter of the present application can be distinguished from this prior art by the fact, that the QD now used are CdS:Mn/ZnS particles.
4. 2. The problem to be solved by the newly claimed contrast agents is to provide new contrast agents for imaging. Already due to their similar nature, the presently claimed contrast agents do not meet the requirements of Article 33.3 PCT for inventive step. Indeed, the physical properties of Se and S in Cd salts are sufficiently similar for the skilled person to use CDS rather than CdSe.
4. 3. Moreover, the missing step for the preparation of CdS:Mn/ZnS particles instead of their CdSe analogues is found in each of documents D3 to D5. Especially D4 also mentions that the CdS:Mn/ZnS particles are prepared following the preparation of CdSe:Mn/ZnS.
4. 4. It would therefore seem, that the present application does not meet the requirements of Article 33.3 PCT for inventive step.

5. For the assessment of the present claims 18-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6. In the present application, no industrial application was found for the cells defined in present claims 41-50. Therefore, these claims do not meet the requirements of Article 33.4 PCT for industrial applicability.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
US2005220714 A1	06-10-2005	21-03-2005	21-03-2005 01-04-2004
WO2005041747 A2	12-05-2005	03-06-2004	03-06-2003 15-08-2003
WO2004066361 A2	05-08-2004	22-01-2004	22-01-2003

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference UF-420XC1	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/015266	International filing date *(day/month/year)* 02 May 2005 (02.05.2005)	Priority date *(day/month/year)* 30 April 2004 (30.04.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant UNIVERSITY OF FLORIDA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- [X] Box No. I — Basis of the report
- [ ] Box No. II — Priority
- [X] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [X] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [ ] Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 17 July 2007 (17.07.2007)
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